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Gastrointestinal–Renal Axis: Role in the Regulation of Blood Pressure

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Hypertension is one of the most common and important health problems worldwide.[1] It has been estimated that 29% of the world's adult population, or 1.56 billion people, will have hypertension by the year 2025.[2] The prevalence of high blood pressure and its adverse consequences result in a heavy burden for hypertensive patients from high-, middle-, and low-income countries.[2,3] Many monogenic causes of hypertension have been reported. However, determining the causes of essential hypertension has been hampered because it is a complex disorder with genetic, epigenetic, and environmental determinants. Among numerous environmental factors, sodium intake is thought to be an important one.

Sodium is essential for cellular homeostasis and fluid balance. However, excessive sodium in the body, as a consequence of increased dietary intake and/or impaired excretion, is the most common risk factor for hypertension.[4] There is overwhelming evidence that high dietary sodium intake increases the risk for incident hypertension and leads to worse cardiovascular outcomes.[4,5] Excess sodium intake also attenuates the beneficial effects of many antihypertensive drugs, including blockers of the renin–angiotensin system (RAS).[6] A modest reduction in dietary salt intake causes a significant fall in blood pressure in both hypertensive and normotensive individuals.[7] Therefore, a low-sodium diet is a major preventive and treatment scheme for hypertension.[8]

The kidney plays a vital role in the regulation of sodium balance and blood pressure. However, the gastrointestinal (GI) tract, which is the organ first exposed to components of food, has taste receptors and sensors for electrolytes (eg, sodium, potassium, phosphate).[9] Therefore, in addition to the kidney, there is increasing realization of the importance of the GI tract in the regulation of sodium balance, and consequently on blood pressure level. For example, GI tract–derived hormones and peptides regulate the autocrine function of renal hormones, affecting renal function, including sodium excretion.[10] We have reported that the GI tract–derived hormone, gastrin, and renal receptors synergistically regulate sodium excretion.[11] In this article, we present an overview of GI tract–mediated regulation of blood pressure, highlight potential strategies for the prevention and treatment of hypertension, and also attempt a look into the future.

Renal Regulation of Sodium Homeostasis

The kidney is crucial in the long-term control of blood pressure by regulating sodium homeostasis.[12] This concept has been confirmed by renal transplantation studies in humans and experimental animals.[13–17] For example, transplantation of kidneys from adult stroke-prone spontaneously hypertensive rats (SPSHR) causes hypertension in normotensive Wistar-Kyoto (WKY) rats, indicating a major role of the kidney in SPSHR hypertension[18]; we have also reported that germline deletion of the D_5 dopamine receptor (D_5R) causes salt-sensitive hypertension. Blood pressure was similar between wild-type mice and wild-type mice transplanted with wild-type kidneys, while blood pressure was higher in wild-type mice transplanted with $D_5R^{-/-}$ kidneys than wild-type kidneys, which also indicates the importance of the kidney in the development of hypertension.[17] All nephron segments of the kidney, including the proximal tubule and medullary thick ascending limb of Henle, participate in the regulation of blood pressure.[19–23] The renal proximal tubule (RPT) is responsible for 65% to 70% of filtered sodium and water reabsorption under normal conditions. Indeed, several studies have shown that human essential hypertension is associated with increased sodium transport in the RPT.[21–23] The inappropriate sodium retention in hypertension results from an enhanced renal sodium transport per se, as well as a failure to respond appropriately to signals that decrease renal sodium transport in the face of increased sodium intake.

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Sodium reabsorption in the RPT is controlled through ion cotransporters/exchangers/pump,[19] such as the sodium glucose cotransporter, sodium amino acid cotransporter, sodium hydrogen exchanger (NHE), sodium phosphate cotransporter type 2, sodium bicarbonate cotransporter, and NBCe2, located at the luminal/apical membrane, and NBCe1 and Na^+-K^+-ATPase located at the basolateral membrane, among others.[19–25] These sodium cotransporters, exchangers, and pump are influenced by numerous neural, hormonal, and humoral factors. These neural, hormonal, and humoral factors can be divided into 2 groups based on their effects on sodium excretion. One group leads to natriuresis, while the other group leads to antinatriuresis (ie, decreased sodium excretion). These 2 groups keep the sodium balance and ultimately blood pressure within the normal range. Renal dopamine and angiotensin II (Ang II), via dopamine receptors or AT_1 receptor, are examples of members of these 2 opposing groups. Thus, in general, activation of renal dopamine receptors leads to diuresis and natriuresis, whereas activation of renal AT_1 receptors leads to antidiuresis and antinatriuresis. In several hypertensive states, dopamine receptor–induced natriuresis is decreased and AT_1 receptor-mediated antinatriuresis is augmented, which consequently lead to sodium retention and hypertension.[12,19–23,26,27]

Salt Sensing and Absorption in the GI Tract

Salt sensing is a complex physiological response. The objective of salt sensing is to keep the sodium balance in the normal range. Indeed, salt sensing occurs in many organs of the body, including the GI tract, from the tongue, stomach, and small and large intestines.[28–33] As aforementioned, the GI tract is the first organ exposed to ingested sodium. In the salt-depleted state, sensing the need for sodium in the tongue and stomach would lead the person to ingest more salt,[34] and in the addition, make the GI tract secrete hormones that increase absorption/reabsorption of sodium in different organs in the body, including the kidney. The converse occurs in the salt-replete state; less salt is ingested and the GI tract triggers the mechanisms to induce natriuresis and diuresis. Sodium given orally is excreted more rapidly than that administered intravenously in many but not all studies.[9,10,35–38] The negative studies should not be taken to dispute the presence of a "gastro-renal reflex" because there are sodium sensors outside the GI tract and kidney (eg, vascular smooth muscles) that "instruct" the kidney to decrease sodium transport.[39] These mechanisms include the recruitment of aversive taste pathways by activating the sour- and bitter-taste-sensing cells, and taste receptors in the kidney.[40–42] Therefore, the targeting of sodium sensors in different parts of the body, including those in the GI tract, may represent new targets for antihypertensive therapy.

Salt Sensing in the Oral Cavity Controls Salt Intake

The oral cavity is the first organ in the GI tract to be exposed to food and nutrients. The taste system is a chemical detection system in the oral cavity, where tastants act as cues for salty, sweet, umami, bitter, and sour tastes on taste buds; a sixth taste (lipid) has also been proposed.[43] A single taste bud contains 50 to 100 taste cells that detect sugars, amino acids, poisons, acids, and minerals. Taste receptors have been identified as ion channels (for salt or sour detection) or G-protein coupled receptors, which are responsive to bitter, sweet, or umami.[44] Interestingly, different from the other 4 tastes, salty taste is unique in that increasing salt concentration fundamentally transforms an innately appetitive stimulus into a powerfully aversive one. This appetitive-aversive balance helps to maintain appropriate salt consumption.[40]

Salt (sodium) can also be sensed by taste receptors, via amiloride-sensitive and -insensitive pathways. Low concentrations (attractive) of NaCl (<100 mmol/L) stimulate the attractive salt taste pathway that is selective for sodium and blocked by amiloride.[40,45,46] High concentration (aversive) of NaCl (>150 mmol/L) is nonselective for sodium and is amiloride insensitive.[45,47] Mice lacking ENaCα selectively in taste receptor cells exhibit a complete loss of salt attraction and sodium taste responses, without affecting taste for sour, bitter, sweet, and umami or the aversive salt pathway.[45] However, high salt in food also recruits the 2 primary aversive taste pathways, ie, sour and bitter, which may have evolved to ensure that high levels of salt reliably trigger robust behavioral rejection, thus preventing its potentially detrimental effect,[40] including hypertension. By contrast, the amiloride-insensitive mechanism, which predominates in circumvallate and foliate taste buds, is involved with a variant of the nonselective cation channel TRPV1 and other salt transduction mechanisms.[47]

The amiloride-sensitive salt taste response is regulated by hormones and humoral factors,[48,49] including Ang II, aldosterone, ghrelin, and insulin.[50,51] Ang II and aldosterone, which are stimulated in states of sodium deficit and are important in the maintenance of a positive sodium balance, also affect salt appetite. The AT_1 receptor and ENaC have been shown to colocalize in a subset of mouse taste bud cells.[50] Whether or not the mineralocorticoid receptor also colocalizes with ENaC in this subset of mouse taste buds has not been shown, but aldosterone has been reported to increase the expression of β and γENaC and ENaC activity in these cells.[51] Shigemura et al suggested that Ang II may increase sodium intake by reducing

amiloride-sensitive taste response that is subsequently suppressed by aldosterone via enhancement of the amiloride-sensitive taste response.[50]

The taste of salt may be altered in hypertension. Some hypertensive patients have higher salt taste sensitivity threshold than normotensives subjects.[52–54] A similar phenomenon may be found in some hypertensive animals. Thus, compared with WKY rats, SHRs have a greater preference for saline and this preference for saline is not related to the existing blood pressure.[55,56] However, Dahl-salt sensitive rats have lower salt intake than Dahl-salt resistant rats.[57] Salt sensitivity of blood pressure also does not correlate with salt appetite in mice.[58] Interestingly, taste sensitivity is decreased in smokers.[46] Impaired taste of salt has been reported to be associated with hypertension in Japanese women; there is a higher prevalence of hypertension in Japanese men married to Japanese women with impaired taste of salt.[59]

GI Tract and Sodium Absorption

The GI tract is responsible for the digestion and absorption of ingested food and nutrients. Another essential function of the GI tract is the coordinated regulation of the secretion and absorption of electrolytes, minerals, and fluids. In healthy adult humans, the GI tract is filled with secreted fluid amounting to 8 to 10 L per day with an additional 1.5 to 2 L per day from ingested food. Most of the electrolytes and fluids are absorbed by the small (≈95%) and large (≈4%) intestines. The intestinal absorption of fluid by GI epithelial cells occurs via active transport of Na^+ and Cl^-[60,61]; NaCl absorption occurs from the small intestine to the distal colon. Healthy adult humans ingest about 250 to 300 mmol sodium per day. However, there is less than 4 mmol sodium in the excrement, suggesting that almost all of NaCl is absorbed in the GI tract. Apparently, there is no difference in sodium absorption between hypertensive patients and healthy controls and Dahl salt-sensitive and salt-resistant rats.[62] Thus, an augmented ability of the intestines to absorb sodium does not participate in the pathogenesis of most cases of hypertension. However, dietary fructose increases sodium absorption by the intestines.[63] Increased intestinal sodium absorption is associated with increased blood pressure in elderly humans.[64] However, NHE activity is increased in the jejunum and ileum of younger (6–9 weeks) but not older (12 weeks) spontaneously hypertensive rats.[65,66] NHE2, NHE3, and NHE8 are found at the brush border membrane of the small intestinal epithelium. Studies in *Nhe2*$^{-/-}$ and *Nhe3*$^{-/-}$ mice have demonstrated that NHE3 accounts for most of the neutral NaCl absorption in the small intestine.[60,67] Inhibition of NHE3 activity only in the GI tract decreased urinary sodium excretion and increased stool sodium by similar amounts but to a lesser degree (≈20–50 mmol sodium/day) in humans than in rats.[61,68] Angiotensin-converting enzyme inhibition by ramipril plus intestinal NHE3 inhibition results in an additive blood pressure–lowering effect.[68] In the colon, sodium absorption is mediated by ENaC; a high salt diet decreases the expression of β and γ ENaC.[69] These suggest that intestinal NHE3 and ENaC blockade could be new treatment strategies for hypertension.

Gut-Derived Hormones, Secreted in Response to Salt Sensors, Modulate Renal Sodium Excretion

The theories and findings underpinning the GI-mediated natriuretic signaling still remain partially solved or incomplete. Nevertheless it is now clear that GI-derived hormones and peptides play important roles in the regulation of renal sodium transport and blood pressure.[10] The GI-derived hormones could be grouped into 3 classes, namely, GI hormones, pancreatic hormones, and GI neuropeptides. According to their ability to affect sodium excretion, we classify these hormones and neuropeptides into 2 classes; 1 increases and the other decreases sodium excretion (Table).[70–101]

In the hypertensive state, GI hormone plasma levels are altered. For example, the basal plasma levels of amylin,[102] glucagon,[103] and insulin[104] are higher, but circulating ghrelin is lower in hypertensive than normotensive humans.[105] We have reported that plasma glucose and insulin levels are not different between salt-resistant and salt-sensitive hypertensive humans. However, oral glucose administration increases plasma insulin levels to a greater extent in salt-sensitive than salt-resistant subjects.[106] The fasting serum gastrin levels are similar in normotensive and hypertensive adult humans, but a mixed meal increased plasma gastrin to greater levels in hypertensive patients than normotensive controls.[107] We have suggested that the greater increase in plasma gastrin in hypertensive than normotensive subjects may be a compensatory response to the impaired natriuretic effect of gastrin, if the studies in the SHRs could be translated to hypertensive humans. In addition, antihypertensive medications also alter circulating GI hormone concentrations.[102,108] It is still unknown what mechanisms produce different GI hormone levels between normotensive and hypertensive status. However, recent studies showed that the inherent differences in gut architecture between WKY rats and SHRs may lead to changes of gut hormones. SHR proximal colon has a mean steady-state modulus almost 3 times greater than WKY rat colon, which is associated with an increase in the vascular smooth muscle cells layer and collagen deposition in the intestinal wall in SHRs.[109] Moreover, the increase in blood pressure in SHRs is also associated with gut pathology such as increasing intestinal permeability and decreasing tight junction proteins.[110] These phenomena that cause stiffening in relation to changes of gut hormones and hypertension is

Table. Summary of Gut-Derived Hormones, Their Receptors, and Functions in Animals and in Renal Cells

Hormone/Peptide	Source	Receptor	Receptor Type	Renal Function in Animals	Renal Site of Hormone Actions	Function in Renal Cells
Promotes natriuresis						
Amylin	Pancreas	Amylin receptor	GPCR	Increases sodium excretion, GFR, and RPF in anesthetized rats[70]	Proximal tubule, distal nephron, juxtaglomerular apparatus	Stimulates proliferation of primary RPT cells from SD rats[71]
Glucagon	Pancreas	Glucagon receptor	GPCR	Inhibits the reabsorption of water and Na^+ in hormone-deprived rats[72]	Proximal tubule	Acutely (1 hour) inhibits, but chronically (24 hours) activates NHE3 activity in OKP cells[73]
Gastrin	Stomach	CCKAR, CCKBR	GPCR	Induces natriuresis and diuresis in WKY rats but not SHRs[11,74]	Proximal tubule	Inhibits NKA and NHE3 activity in RPT cells from WKY rats and human[11,75]
Ghrelin	Stomach	GHSR	GPCR (GHSR1a), a 5-transmembrane spanning form, GHSR1b	Promotes diuresis and renal nitric oxide production in Dahl salt-sensitive hypertensive rats[76]; stimulates distal nephron-dependent sodium reabsorption in SD rats[77]	Distal nephron	Reduces mitochondria membrane potential and mitochondria-derived ROS, ameliorates Ang II-induced cell senescent in RPT cells (HK-2 cell line)[78]
CCK	Duodenum	CCKAR, CCKBR	GPCR	Induces diuresis and natriuresis in anesthetized SHRs[79]	Proximal tubule	…
Uroguanylin	Duodenum and jejunum	Guanylate cyclase-C	Guanylyl cyclase family	Induces natriuresis, kaliuresis, and diuresis in male Wistar rats[80]; inhibits bicarbonate reabsorption in male Wistar rats[81,82]	Proximal tubule, renal distal tubule	Inhibits the NHE3 activity in RPT cells (LLC-PK_1 cell line)[81] and H^+-ATPase activity and surface expression in MDCK-C11 cells[82]
Guanylin	Duodenum and colon	Guanylate cyclase-C	Guanylyl cyclase family	Causes kaliuresis and diuresis with less pronounced natriuretic effect in male Wistar rats[80]	Collecting duct	Inhibits luminal K^+ channels in human CCD cells[83]
Secretin	Duodenum and jejunum	Secretin receptor	GPCR	Increases both urinary volume and sodium excretion in healthy male volunteers[84]	Thick ascending limb of the loop of Henle	…
VIP	The whole small intestine	VIP receptor	GPCR	Increases the excretion of sodium, chloride, potassium, and fluid in male SD rats[85]	Proximal tubules	Decreases the intracellular ROS levels in HK2 human renal cells[86]; stimulates adenylate cyclase activity in canine renal epithelial (MDCK) cells[87]
GLP-1	Distal small intestine	GLP-1 receptor	GPCR	Inhibits sodium uptake,facilitates natriuresis in male Wistar rats[88]	The brush border of proximal tubules	Inhibits the NHE3 activity and sodium reabsorption in RPT cells (LLC-PK_1 cell line) and primary porcine RPT cells[89,90]

Continued

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Hormone/Peptide	Source	Receptor	Receptor Type	Renal Function in Animals	Renal Site of Hormone Actions	Function in Renal Cells
PYY	Intestinal mucosa of the ileum and large intestine	Y receptors (Y1-Y5)	GPCR	Increases sodium excretion, decreases GFR and RBF in male subjects and Wistar rats[91,92]	Proximal tubules	Stimulates cell growth of mouse RPT cells[93]
Promotes sodium retention						
Insulin	Pancreas	Insulin receptor	Tyrosine kinase receptor	Stimulates sodium and volume absorption in the rabbit kidney[94]	RPTs, the TALH, the distal convoluted tubule and the connecting tubule	Stimulates sodium transporters including NKA and NHE3 in OK cells and in primary RPT cells from SD rats[95,96]
C-peptide	Pancreas	…	…	Attenuates high salt-induced urine albumin, glomerular permeability, renal inflammation in the Dahl salt-sensitive rat[97]	Proximal tubules, medullary thick ascending limb	Stimulates NKA in human RPT cells[98]
IGF-1	Liver	IGF receptor	Tyrosine kinase receptor	Increases GFR and RPF, and decreases renal vascular resistance in WKY rats, but not in SHRs[99]; inhibits the basolateral Cl channels in SD rats[100]	RPT,thick ascending limb collecting ducts	Stimulates ClC-K2 channels, promotes net Na^+ and Cl^- reabsorption in mouse CCD cells[101]

Ang II indicates angiotensin II; CCD, cortical collecting ducts; CCKAR, cholecystokinin A receptor; CCKBR, cholecystokinin B receptor; GFR, glomerular filtration rate; GHSR, growth hormone secretagogue receptor; GLP-1, glucagon-like peptide-1; GPCR, G-protein coupled receptor; IGF, insulin-like growth factor; MDCK, Madin-Darby canine kidney; NHE3, Na^+-H^+ exchanger 3; NKA, Na^+-K^+-ATPase; OKP cells, opossum kidney proximal tubule cells; PYY, peptide YY; RBF, renal blood flow; ROS, reactive oxygen species; RPF, renal plasma flow; RPT, renal proximal tubule; SD rats, Sprague-Dawley rats; SHRs, spontaneously hypertensive rats; TALH, thick ascending limb of Henle; VIP, vasoactive intestinal peptide; WKY rats, Wistar Kyoto rats.

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unknown. However, these changes in gut pathology in hypertension are associated with alterations of gut microbiota,[110] which has been reported to play an important role in the regulation of gut or renal hormones/peptides (vide infra).

In the kidney, there are also differences of GI hormone levels and their receptor expression and function between the hypertensive and normotensive state. For example, renal amylin receptor expression is increased[111] but renal glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) expression is decreased in SHRs and hypertensive patients.[112] The renal expression of insulin receptors is not different between WKY and SHRs, but a high-salt diet decreases insulin receptor expression in WKY but not SHRs.[113] Of note is that insulin-resistant rats have decreased renal insulin expression.[114] We have reported that there is no difference of cell surface membrane expression of gastrin receptor, also called cholecystokinin (CCK) B receptor (CCKBR), in RPT cells between WKY rats and SHRs. However, the infusion of gastrin induces a natriuresis and diuresis in WKY rats but not in SHRs.[11] Gastrin inhibits Na^+-K^+-ATPase activity in RPT cells from WKY rats but not SHRs.[11] However, gastrin-containing cells are increased in the stomach of SHRs and rats with renovascular hypertension.[115,116]

In this report, we only discuss 2 GI hormones, gastrin and GLP-1, which have received increasing attention because of their ability to regulate renal sodium handling and blood pressure, by themselves and in interaction with other hormones.

Glucagon-Like Peptide-1

GLP-1 is secreted by intestinal L-cells. Under normal conditions, GLP-1 is rapidly degraded at the N-terminal penultimate position by dipeptidyl peptidase-4. There is no difference in circulating levels of GLP-1 between young (5-week-old) WKY and SHRs. However, there is a nonsignificant trend towards a decrease in plasma levels of total GLP-1 in adult (20-week-old) SHRs compared to adult WKY rats, which may be because of the higher plasma level and activity of dipeptidyl peptidase-4 in SHRs than age-matched WKY rats.[117] The actions of GLP-1 are primarily mediated by its receptor GLP-1R, which is widely distributed throughout the body, including the kidney. GLP-1R is expressed in the brush border of RPT. In rodents, GLP-1R stimulation suppresses RPT sodium transport, resulting in a natriuresis,[88] which is also aided by GLP-mediated increase in glomerular filtration rate in rodents. GLP-1R is constitutively active because the intravenous administration of exendin-9, a GLP-1R antagonist, decreased glomerular filtration rate, lithium clearance, urine flow, and sodium excretion in male Wistar rats. The inhibition of RPT sodium transport by GLP-1 is caused by inhibition of NHE3 activity via a protein kinase A–dependent mechanism.[88] GLP-1R expression is decreased in renal arteries of SHRs and hypertensive patients.[112] GLP-1R antagonist exendin 9 to 39 inhibits GLP-1R-mediated relaxation in WKY arteries, whereas the relaxations are significantly less in SHR arteries.[112] GLP-1 has antihypertensive effects that may be related to both an increase in sodium excretion and vasodilatory effect in rodents.[118]

In humans, as in rodents, GLP-1 induces natriuresis in healthy subjects and in insulin-resistant obese men.[119,120] GLP-1-mediated natriuresis in humans is related to inhibition of renal proximal sodium transport.[119] However, in contrast to rodents, the natriuretic effect of GLP-1 is not associated with an increase in renal plasma flow or glomerular filtration rate.[119,120] The natriuretic effect of GLP-1 in humans is also associated with a decrease in plasma Ang II but not plasma renin, aldosterone, or urinary excretion of angiotensinogen.[119] The natriuretic and antihypertensive effect of exendin-4, a GLP-1 agonist, is also related to a decrease in renal Ang II concentration in salt-sensitive obese db/db mice.[121] Exendin-4 also prevents Ang II-induced hypertension in nondiabetic mice.[121] A synergism between GLP-1 and atrial natriuretic peptide is found in rodents but not in humans.[122] In a 24-week, double-blind, placebo-controlled, parallel-group study at 23 centers, exenatide, a GLP-1 agonist, reduced systolic and diastolic blood pressure.[123] Similar results were found with ambulatory blood pressure.[124] A meta-analysis of clinical trials including 16 randomized controlled trials that enrolled 3443 patients showed that treatment with the GLP-1R agonist reduced systolic and diastolic blood pressure in patients with type 2 diabetes.[125] Another meta-analysis also showed a beneficial effect of GLP-1R agonists on major cardiovascular events.[126]

The above studies would suggest that GLP-1 would have an antihypertensive action. Indeed, in humans and mice GLP-1 has antihypertensive effects.[124,127,128] However, several studies in rats have reported that GLP-1 injection increases blood pressure in a short time.[129,130] The reason may be associated with the fact that GLP-1 also acutely increases heart rate and cardiac output, and activates autonomic regulatory neurons.[129,131] Plasma levels of GLP-1 have been associated with systolic and diastolic blood pressure in awake and sleeping healthy human subjects.[132] The positive correlation between plasma GLP-1 and blood pressure was not related to blood glucose or insulin but could be related to insulin resistance.

Decreased GLP-1 and renal GLP-1R expression may be involved in the pathogenesis of hypertension. As stated above, renal arteries from SHRs and humans with essential hypertension have decreased GLP-1Rs, and GLP-1-mediated renal arterial vasorelaxation is impaired in SHRs.[112] In rats, serum level of GLP-1, as well as renal GLP-1R expression, is decreased in N(G)-nitro-L-arginine methyl ester (L-NAME)-induced hypertension, relative to controls.[133] Sitagliptin, a dipeptidyl peptidase-4 inhibitor, protects against L-NAME-

induced hypertensive nephropathy by increasing the serum level of GLP-1 and upregulation of GLP-1 receptors.[133]

CCK and Gastrin

Gastrin is mostly synthetized in the G cells in the mucosa of the gastric antrum. Small amounts are produced in the mucosa of the jejunum and outside the GI tract, such as a few cerebral and peripheral neurons, pituitary gland, and spermatocytes.[134–136] CCK, unlike gastrin, is synthesized by I cells in the upper intestine, but share the same receptors, CCK receptor type A (CCKAR) and CCKBR. CCKAR is characterized by a high affinity for CCK and by a low affinity for gastrin; in contrast, CCKBR has a similar affinity for both peptide hormones. Because plasma gastrin levels are much higher than CCK, CCKBR is also considered a gastrin receptor.[137] The CCKBR is expressed in specific nephron segments, including the proximal tubule, distal tubules, and collecting ducts.[74,138] We have reported that CCKBR mRNA but not CCKAR is expressed in human RPT cells.[75] In the isolated perfused rat kidney, it is the CCKBR, not CCKAR, that mediates the increase in sodium and decrease in potassium excretion caused by the infusion of gastrin-17.[74]

Both CCK and gastrin induce natriuresis and diuresis.[11,74,79,134] CCK may not increase glomerular filtration rate[79] but can increase renal blood flow that is blunted in obese-prone and hypertensive rats.[139] Although both CCK and gastrin exert similar effects in kidney, circulating gastrin levels are 10- to 20-fold higher than CCK.[140] Circulating CCK levels are not or transiently increased by gastric distention or duodenal saline infusion.[141] Moreover, CCK in the circulation is rapidly degraded by aminopeptidases.[142] Of all the gut hormones, gastrin is the one that is taken up to the greatest extent by RPTs.[143] Food (with Na^+) increases serum gastrin levels, and Na^+ given orally, even without food, also increases serum gastrin levels.[144] Therefore, gastrin may be a better candidate than CCK as the effector of the gastro-renal reflex, at least regarding sodium balance.

The importance of gastrin in the regulation of sodium excretion and blood pressure is also supported by the gastrin (Gast) gene-deficient mice ($Gast^{-/-}$). $Gast^{-/-}$ mice do not increase their sodium excretion after ingestion of sodium and develop salt-sensitive hypertension.[145] We and others have reported the diuretic and natriuretic effects of gastrin in both rats and humans.[11,74,134,146] This may be related to the ability of gastrin to inhibit Na^+-K^+-ATPase and NHE3 activities in RPT cells.[11,75,147] Moreover, the inhibition of renal sodium transport by gastrin may be tissue specific because gastrin increases H^+-K^+-ATPase activity in gastric parietal cells.[148] Our studies also showed that the diuretic and natriuretic effects of gastrin, as well as its inhibitory effect on Na^+-K^+-ATPase activity, are lost in SHRs, suggesting that aberrant regulation of gastrin on the natriuresis may have a role in the pathogenesis of hypertension.[11,149] The fasting serum gastrin levels are similar in normotensive and hypertensive adults; however, the increase of serum gastrin levels is higher in the latter group than in the former group after a mixed meal.[107]

Effects of Bariatric Surgery on the Secretion of GI-Derived Hormones and Blood Pressure

Bariatric surgery may affect the secretion of gut-derived hormones and blood pressure. Different surgical methods may have different effects on the secretion of the same GI hormone. For example, fasting plasma gastrin levels are normal in laparoscopic gastric bypass surgery,[150] while sleeve gastrectomy results in increased fasting plasma gastrin levels.[151] The postprandial gastrin secretion induced by a mixed meal is also enhanced by sleeve gastrectomy.[152] By contrast, procedures that reroute the nutrient passage to the intestines, bypassing the gastric antrum, such as Roux-en-Y gastric bypass (RYGB), prevent the increase in plasma gastrin following a mixed meal.[152–154]

Depending on the subjects or postoperative time, bariatric surgery has different effects on the GI hormone responses. The first 2 weeks after RYGB in obese nondiabetic subjects, fasting plasma levels of insulin, ghrelin, and peptide YY (PYY) are decreased, but insulin sensitivity increased.[153] The postprandial response to a mixed meal is increased for C-peptide, GLP-1, GLP-2, PYY, CCK, and glucagon; by contrast, the postprandial response was decreased for ghrelin, leptin, and gastrin and unchanged for glucose-dependent insulinotropic polypeptide, amylin, pancreatic polypeptide, and somatostatin.[153] In obese patients with type 2 diabetes, 15 days after RYGB, fasting plasma levels of pancreatic polypeptide, glucagon, and GLP-1 are increased; but the pancreatic polypeptide response to a mixed meal is decreased while that of glucagon and GLP-1 remains increased.[155] After 1 year in these same patients, PYY response to a mixed meal is increased, while amylin, ghrelin, and GLP-1 are decreased.[155] The same study also found that the hormonal responses after sleeve gastrectomy are similar to those with RYGB except that fasting and meal-induced plasma pancreatic polypeptide levels remain increased but unchanged for amylin.[155]

Both long-term and short-term studies have shown that the blood pressures are decreased in adults and adolescents who underwent bariatric surgery, such as RYGB and sleeve gastrectomy.[156–158] Compared with RYGB, sleeve gastrectomy is associated with better early remission rates for hypertension and improvement in insulin sensitivity.[159,160] This may be related to the ability of bariatric surgery to increase the plasma levels of natriuretic enterokines such as GLP-1,[155,160,161] which is natriuretic.[88,118,119] In a study of 33 patients that lasted for 14 to 41 months after RYGB, 11 had

increased sodium excretion while 22 had decreased sodium excretion that was related to "excess weight loss" and could also have been related to decreased sodium intake.[162,163] Rats that are undergoing RYGB surgery also have increased sodium excretion following oral salt loading.[164] The decrease in glomerular filtration from high values with bariatric surgery could also be considered a beneficial rate.[165,166]

Interaction Between GI and Renal Hormones in the Regulation of Blood Pressure

Depending on the state of sodium balance, an oral NaCl load may induce a greater natriuresis and diuresis than an intravenous infusion of the same amount of NaCl in some but not all studies.[35–38] As stated above, the negative studies should not be taken to dispute the presence of a "gastro-renal axis" because there are sodium and chloride sensors[167] outside the GI tract and kidney (eg, vascular smooth muscles, heart, and nervous system) that "instruct" the kidney to decrease sodium transport.[29,168,169]

Interaction Between GI Hormones and Renal Dopamine

Dopamine, a neurotransmitter in neural tissue, also acts as an autocrine/paracrine substance in nonneural tissues including the kidney. Dopamine, produced locally in the kidney, is now recognized to serve an important role in the regulation of blood pressure and sodium balance by direct actions on renal and intestinal epithelial ion transport, interaction with other receptors, and modulation of the secretion of hormonal/humoral agents.[26,170–174] Dopamine receptors are classified into D_1- and D_2-like receptor subtypes: D_1-like receptors (D_1R and D_5R) couple to stimulatory G protein $G\alpha S$ and stimulate adenylyl cyclase activity, whereas D_2-like receptors (D_2R, D_3R, and D_4R) couple to inhibitory G protein $G\alpha i/G\alpha o$ and inhibit adenylyl cyclase activity. These receptors can also couple to other G protein subunits, including Gq and Golf.[175–177] All of the 5 dopamine receptor subtypes are expressed in the nephron. Disruption of any of the dopamine receptor genes in mice results in hypertension, the pathogenesis of which is specific for each receptor subtype.[173] In hypertensive states, dopamine receptor–mediated natriuresis and diuresis are impaired. The dopaminergic effect on renal water and sodium transport is modulated by interaction with GI hormones (vide infra).

CCK/Gastrin and Dopamine Interaction

Gastrin is the major GI hormone taken up by RPT cells.[143] Disruption of gastrin receptor (CCKBR) in mice caused hypertension and decreased sodium excretion.[178] We tested the hypothesis that gastrin may interact with renal dopamine receptors to increase sodium excretion, an impairment of which may result in hypertension.[11,178] We found that gastrin synergistically interacts with renal D_1-like receptors to increase water and sodium excretions in normotensive WKY rats, effects that were not observed in SHRs. The interaction between gastrin and dopamine in the kidney occurred at the receptor level because blockade of D_1-like or CCKBR abolished the natriuresis and diuresis caused by gastrin or D_1-like receptor agonist fenoldopam, in WKY rats and BALB/c mice.[11,178] The gastrin/D_1-like receptor interaction was confirmed in RPT cells. In RPT cells from WKY but not SHRs, stimulation of either D_1-like receptor or CCKBR inhibited Na^+-K^+-ATPase activity, an effect that was blocked by D_1-like receptor or CCKBR antagonist.[11] We also found that CCKBR colocalized and coimmunoprecipitated with D_1R or D_5R in RPT cells, which was increased after stimulation of either D_1-like receptor agonist or gastrin.[11,178] Moreover, stimulation of 1 receptor increased the RPT cell membrane expression of the other receptor, effects that were not observed in SHRs.[11] The natriuresis induced by a high sodium diet can also be blocked by D_1-like receptor agonist or CCKBR antagonist.[178] These data suggest that there is a synergism between CCK_BR and D_1R or D_5R to increase sodium excretion. An aberrant interaction between the renal CCK_BR and both D_1-like receptors may play a role in the pathogenesis of hypertension.

Insulin and Renal Dopamine Interaction

Insulin is secreted from pancreatic β cells, and exerts its physiological functions via its receptors. Insulin receptors are widely distributed in the kidney and affect multiple aspects of renal function. Besides its action on glucose metabolism, insulin acts on almost all of the nephron segments and has been associated with anti-natriuresis at the whole-animal level, sodium retention in isolated, perfused tubule studies, and sodium uptake in cell culture.[179–181] In kidney, insulin stimulates sodium and volume absorption by directly stimulating some specific sodium transporters, exchangers, and channels in renal tubule segments.[179–181] Compensatory hyperinsulinemia in individuals with insulin resistance enhances salt absorption in the RPT, resulting in a state of salt overload and hypertension. On the other hand, a high sodium diet causes an increase in insulin resistance.[182]

Insulin and dopamine have counterregulatory effects on renal sodium transport. Insulin interacts with dopaminergic system at 2 different levels in the kidney. First, insulin positively regulates the uptake of L-dihydroxyphenylalanine, the immediate precursor of catecholamines, including dopamine, through the increase in the number of high-affinity transport sites in the RPT.[183] Second, insulin impairs

dopamine receptor expression and function in the kidney. Studies in both RPTs from hyperinsulinemic animals and renal cell cultures treated with insulin show reduced D_1R number, defective receptor-G protein coupling, and blunted D_1-like agonist-induced Na^+-K^+-ATPase inhibition.[184,185] Moreover, insulin resistance leads to hyperphosphorylation of D_1R and their uncoupling from Gs proteins in obese Zucker rats, which can be restored by an insulin sensitizer, rosiglitazone.[186] It is possible that the insulin-mediated increase in RPT cell uptake of L-dihydroxyphenylalanine could be a compensatory mechanism for the insulin-mediated blunting of D_1R function.

In addition to the interaction between insulin and D_1R, insulin also interacts with D_5R and D_2R. Insulin increases D_5R expression and its mediated inhibition of Na^+-K^+-ATPase activity in RPT cells, which may be an important counterbalance to the increase in renal tubular sodium reabsorption induced by insulin. However, the compensatory increase in D_5R expression following insulin treatment is lost in RPT cells from SHRs.[187] Dopamine also regulates insulin receptor expression and function. Thus, the D_1-like receptor agonist fenoldopam increases the expression of insulin receptor in human RPT cells. Moreover, D_1R interacts with sorting nexin 5 to increase the sensitivity to insulin via a positive regulation of insulin receptor expression and insulin signaling.[188] Additionally, activation of D_2R also regulates insulin secretion. Acute administration of a D_2-like receptor agonist quinpirole or an agonist bromocriptine inhibits glucose-stimulated insulin secretion by a D_2R-dependent or -independent mechanism.[189,190] Disruption of the D_2R in mice also shows the impaired insulin secretion and glucose intolerance.[191]

Interaction Between GI Hormones and the RAS

It is well known that the RAS plays a key role in the development and maintenance of hypertension.[192,193] The classical view of the products of the RAS as a circulating hormone has evolved to organ-based systems that perform paracrine/autocrine functions. Local RAS exists in different organs including the kidney. Ang II is classically considered the main mediator of the RAS. The renal tubules and interstitial compartments contain much higher levels of Ang II than plasma.[194] The majority of intrarenally produced Ang II functions as a paracrine hormone. AT_1R mediates the vast majority of renal actions of Ang II, including renal tubular sodium transport.[27] The RAS is broadly activated in hypertensive status, including increased angiotensin-converting enzyme activity and Ang II levels in plasma, and enhanced renal AT_1R expression and intrarenally generated Ang II.[195,196] The counteraction of some endogenous factors may be novel therapies to combat RAS-dependent hypertension. There are increasing evidences of interactions between intrarenal RAS and the GI-derived hormones in the kidney.

GLP-1 and the RAS

GLP-1 can interact with the RAS.[119,121,122] GLP-1R agonists counteract the hypertensive action of Ang II. Rodent studies have shown that GLP-1R stimulation ameliorates Ang II-induced hypertension.[121,122] Exendin-4, a GLP-1R agonist, attenuated Ang II-induced high-salt sensitivity and minimized the increase in blood pressure caused by Ang II infusion.[121] Another GLP-1R agonist, liraglutide, also normalized both systolic and diastolic blood pressure in mice with Ang II-induced hypertension.[122] Exendin-4 was also reported to decrease the Ang II-induced ERK1/2 phosphorylation in opossum RPT cells.[121]

There is also evidence of a renal beneficial role of the combination of GLP-1R agonists with inhibitors of the RAS components, such as angiotensin-converting enzyme inhibitors and Ang II receptor blockers. An exenatide analog, AC3174, lowered blood pressure in Dahl salt-sensitive rats fed a high-salt diet. Moreover, the ability of AC3174 to attenuate renal damage was enhanced by captopril, an angiotensin-converting enzyme inhibitor, in these Dahl salt-sensitive rats that were fed a high salt diet.[197] The combination of an Ang II receptor blocker (telmisartan) and a dipeptidyl peptidase-4 inhibitor (linagliptin) reduced urinary albumin excretion and renal oxidative stress in diabetic endothelial nitric oxide synthase knockout mice, indicating that linagliptin in addition to an Ang II receptor blocker may be a new therapeutic approach for patients with diabetic nephropathy.[198]

A randomized, double-blinded, single-day, crossover trial showed that the infusion of GLP-1 in healthy young males decreased Ang II but not plasma renin or aldosterone levels or urinary excretion of angiotensinogen.[119] However, the intravenous administration of GLP-1 increased aldosterone secretion in rats.[199]

The Role of Gut Microbiota in the Regulation of Gastro-Renal Axis and Blood Pressure

In recent years, an increasing number of studies have focused on the association between gut microbiota and cardiovascular diseases, including hypertension. There is a significant decrease in gut microbial richness, diversity, and evenness in addition to an increase in the Firmicutes/Bacteroidetes ratio in the SHRs and a small cohort of human hypertension patients.[200] The oral administration of minocycline attenuates high blood pressure, and rebalances the dysbiosis of gut microbiota in the Ang II infusion hypertension model by reducing the Firmicutes/Bacteroidetes ratio.[200] Similar differences of gut microbiotal genomic composition have been found between the Dahl salt-sensitive and Dahl salt-resistant rats.[201] High blood pressure is induced in WKY rats after

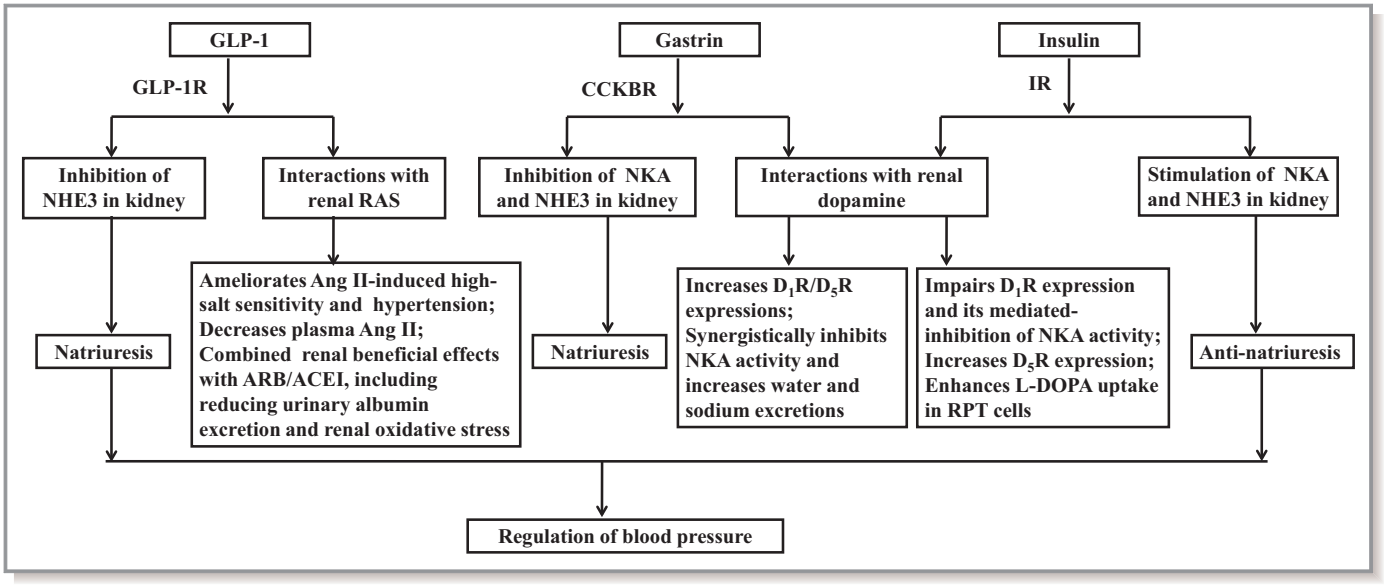

Figure. Schematic representation of the interaction of gut-derived hormones with renal hormones/peptides in the regulation of natriuresis and blood pressure. ACEI indicates angiotensin converting enzyme inhibitor; Ang II, angiotensin II; ARB, angiotensin II receptor blocker; CCKBR, cholecystokinin A receptor; D_1R, dopamine D_1 receptor; D_5R, dopamine D_5 receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; IR, insulin receptor; L-DOPA, L-dihydroxyphenylalanine; NHE3, Na^+-H^+ exchanger 3; NKA, Na^+-K^+-ATPase; RAS, renin–angiotensin system; RPT, renal proximal tubule.

exchanging the gut microbiota between the WKY rats and SHRs.[202] Gut microbial metabolites, such as short-chain fatty acids (SCFAs), were found to influence host physiological functions including blood pressure.[203] SCFAs influence blood pressure via activating sensory receptors such as olfactory receptor 78 (Olfr78), GPR41, and GPR43.[203,204] Olfr78 is expressed well in the renal juxtaglomerular apparatus, where activation of Olfr78 induces renin secretion. Treatment with antibiotics reduces the biomass of the gut microbiota and elevates blood pressure in Olfr78 knockout mice.[205] These studies indicate the role of gut microbiota in the pathophysiology of hypertension.

Although the mechanisms of gut microbiota on regulation of blood pressure are complex, effects on gut or renal hormones/peptide synthesis or release might be involved. The gut microbiota, via various metabolites such as SCFA, can influence the number and function of enterochromaffin cells, thereby promoting the release of serotonin that in turn impacts host physiological functions.[206] It is reported that gut microbiota affect the generation of free dopamine and norepinephrine in the gut lumen.[207] The levels of dopamine and norepinephrine in the lumen of the cecum are higher in control mice than the germ-free mice.[207] The absence of the gut microbiota has been reported to exacerbate the neuroendocrine and behavioral responses to acute stress and decreased dopamine turnover in the frontal cortex, hippocampus, and striatum in response to acute stress in F344 rats.[208] However, in BALB/c mice, administration of oral antimicrobials increases exploratory behavior that is independent of changes in levels of GI neurotransmitters such as serotonin, dopamine, and norepinephrine.[209] In addition, SCFAs, via activation of Olfr78, induce renin release from the afferent arteriole and increase blood pressure, which is confirmed in Olfr78-deficient mice displaying lower renin concentrations, and decreased blood pressure.[205] Resistant starch is fermented to SCFAs by microflora in the large intestine. High-amylose resistant starch is associated with increased gene expression of proglucagon (gene for GLP-1) and PYY in the cecal and large intestine, and increased plasma levels of PYY and GLP-1, which play important roles in the regulation of blood pressure.[210] Dietary factors such as high fiber diet, and acetate supplementation change the gut microbiota, down-regulate renal RAS, and prevent the development of hypertension in desoxycorticosterone acetate–salt hypertensive mice.[211] These indicate that targeting the gut microbiota may be a potential and novel strategy for the regulation of gastro-renal axis and treatment of hypertension.

Conclusions and Perspectives

In summary, increasing evidences support the concept of a gastro-renal communication in the excretion of a sodium load. Enterokines are released from the intestine into the circulation in response to sodium intake that interacts with dopamine receptors in the kidney to regulate sodium excretion and keep the blood pressure in the normal range (Figure). The aberrant gastro-renal natriuretic signaling axis may be involved in the pathogenesis of hypertension.

Increased understanding of the role of the gastro-renal axis in the regulation of renal function may give us a novel insight into the pathogenesis of hypertension and provide a new treatment strategy for hypertension.

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Disclosures

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